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ORIGINAL RESEARCH

Evaluating the role of a ^{99m}Tc-HYNIC-PSMA SPECT scan following a negative bone scan in men with prostate cancer: a single-centre, retrospective cohort study

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Purpose: This study aimed to review the management of patients with high-risk and unfavourable intermediate-risk prostate cancer, who had a ^{99m}Tc-HYNIC-PSMA SPECT (technetium-99m hydrazine nicotinamide prostate-specific membrane antigen single-photon emission computerised tomography) scan following a negative ^{99m}Tc-MDP (technetium-99m methylene diphosphonate) bone scan.

Materials and methods: This study is a retrospective review of patients with high-risk and unfavourable intermediate-risk prostate cancer, who underwent a ^{99m}Tc-PSMA SPECT scan after a negative/equivocal bone scan between January 2018 and December 2020. Patients with a life expectancy of less than 10 years were excluded.

Results: A total of 64 patients were investigated. The mean age was 63 years and the mean prostate-specific antigen (PSA) level was 40 ng/mL. The International Society of Urological Pathology (ISUP) scores were as follows: ISUP 1 in six patients, ISUP 2 in eight patients, ISUP 3 in 13 patients, and ISUP > 4 in 37 patients. A positive ^{99m}Tc-PSMA SPECT scan for disease metastases occurred in 20% of the patients who had a negative bone scan. Seven of the patients with a positive ^{99m}Tc-PSMA SPECT scan received a bilateral orchiectomy, while four patients received treatment with radical intent. Management of patients with both scans negative included external beam radiotherapy (EBRT) and androgen deprivation therapy (ADT) (n = 47), and radical prostatectomy with or without lymph node (LN) dissection (n = 4). A limiting factor was that not every patient underwent conventional cross-sectional imaging of the pelvis and prostate prior to intervention.

Conclusion: A ^{99m}Tc-PSMA SPECT scan is a valuable diagnostic tool and was able to identify one in five men (20%) who are understaged by bone scan, allowing for their management plan to be tailored and sparing them morbid intervention.

Keywords: prostate cancer, bone scan, ^{99m}Tc-PSMA SPECT scan, staging, management

Introduction

Prostate cancer is the second most common cause of cancer deaths among men. It is estimated that one in seven (15.3%) men will be diagnosed with prostate cancer, and one in 38 (2.6%) will die from this disease.[1] Prostate cancer can be risk stratified into low risk, intermediate risk (favourable and unfavourable), and high risk for disease progression per modified Epstein criteria.[2] These stratifications are based on the PSA level, digital rectal examination, and Gleason score from a prostate biopsy.

For intermediate-risk and high-risk patients, imaging plays an important role in the management of prostate cancer with curative intent. Investigations help plan treatment selection, including radical prostatectomy and level of LN dissection or EBRT. Current European Association of Urology (EAU) guidelines recommend abdominopelvic imaging and bone scan for patients with high-risk diseases.[3] The 2022 National Comprehensive Cancer Network (NCCN) guidelines indicate that for patients with high-risk prostate cancer, next-generation imaging – whole-body magnetic resonance imaging (MRI), prostate-specific membrane antigen positron emission tomography (PSMA PET) – should be performed if results from conventional imaging modalities – computed tomography (CT), multiparametric MRI, or bone scan – are negative or equivocal.

The ^{68}Ga-PSMA PET/CT (gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography) is a non-invasive diagnostic technique to image prostate cancer with increased Prostate Specific Membrane Antigen (PSMA) expression. Nearly all adenocarcinomas of the prostate demonstrate PSMA expression in the majority of primary and metastatic lesions.[4,5] Research has shown that PSMA expression is a significant prognosticator for disease outcomes.[6] Several studies demonstrate the superiority of the ^{68}Ga-PSMA PET/CT compared to CT, MRI, or a bone scan for the detection of metastases at initial staging at primary diagnosis.[7–11] However, the ^{68}Ga-PSMA PET/CT is more expensive and not always readily available. Our study involves the ^{99m}Tc-HYNIC-PSMA, which is more readily available and significantly cheaper.

This study reviewed how patients were managed (radical prostatectomy, radiotherapy, or bilateral orchiectomy) following a ^{99m}Tc-PSMA SPECT scan after a previously negative ^{99m}Tc-MDP bone scan.

Materials and methods

This study was a retrospective review of the imaging and staging protocols implemented and how they affected management decisions at the Groote Schuur Hospital in Cape Town, South Africa, between January 2018 and December 2020. The study population consisted of patients with high-risk and high-tier (unfavourable) intermediate-risk prostate cancer, with high-risk defined as greater than or equal to clinical stage T2c, or a PSA level ≥ 20 ng/mL, or

Gleason score 8–10.[12] High-tier (unfavourable) intermediate-risk prostate cancer was defined as Gleason score 4 + 3, or more than one intermediate risk factor (T2b and/or Gleason score = 7 and/or PSA > 10–20 ng/mL not low-risk), or greater than 50% positive biopsy cores.[13] All patients were staged at a prostate cancer multidisciplinary team meeting, where decisions regarding whether or not a patient is eligible for radical therapy are made.

Inclusion and exclusion criteria

Inclusion criteria consisted of high-risk and high-tier intermediate-risk prostate cancer patients who had a bone scan and a ^{99m}Tc-PSMA SPECT scan between October 2018 and January 2020.

The exclusion criteria consisted of:

- patients who are not candidates for radical treatment (life expectancy less than 10 years, multiple comorbidities);
- low-risk and low-tier (favourable) intermediate-risk prostate cancer patients; and
- confirmed metastases on previous plain film, CT or MRI.

Recruitment and enrolment

All patients enrolled in the study had been recruited from the combined Urology and Oncology multidisciplinary team, which took place at LE34 at the Groote Schuur Hospital. Figure 1 illustrates the patient recruitment and enrolment process. All the enrolled patients would have had both a ^{99m}Tc-MDP bone scan as well as a ^{99m}Tc-PSMA SPECT scan performed at the Nuclear Medicine Department. Results from these studies were provided by Nuclear Medicine physicians. Upon enrolment into the study, the patients were assigned a patient number, and this number was included in the patient data sheet. Patient folders were reviewed, and the management they underwent was evaluated – whether it was curative (radical prostatectomy or radiotherapy) or alternate.

Research procedures and data collection methods

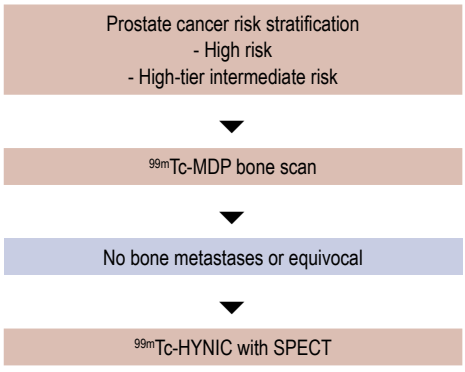

Figure 1: Patient recruitment and enrolment

A protocol based on the NCCN guidelines was agreed upon between the Nuclear Medicine and Oncology Departments, which stated that all high-risk and high-tier intermediate-risk prostate cancer patients who are candidates for radical treatment will undergo a bone scan followed by a ^{99m}Tc-PSMA SPECT scan if the bone scan was negative or equivocal. The folders of patients eligible for the study were reviewed, and management was examined.

Results

A total of 64 patients underwent both a bone scan and a ^{99m}Tc-PSMA SPECT scan. Their baseline characteristics are summarised in Table I. The majority, 50 patients, were risk stratified as having high-risk prostate cancer, while the remaining 14 patients had unfavourable intermediate-risk cancer. There were 13 patients with a negative bone scan and a positive ^{99m}Tc-PSMA SPECT scan for disease metastases, with six having disease at more than one metastatic site. Sites of metastases included LN (*n* = 12), bone (*n* = 3), and visceral organs (*n* = 3).

Eight of the patients with a positive ^{99m}Tc-PSMA SPECT scan received a bilateral orchiectomy. Five patients received treatment with radical intent, including EBRT and ADT (*n* = 4), and radical prostatectomy with extended pelvic LN dissection (*n* = 1). Management of those patients with both a negative bone scan and a ^{99m}Tc-PSMA SPECT scan included EBRT and ADT (*n* = 47) and radical prostatectomy with or without LN dissection (*n* = 4). A total of five patients underwent radical prostatectomy (including one with a positive ^{99m}Tc-PSMA SPECT scan for metastases). Of these, only two received a pelvic LN dissection. Histology findings correlated with preoperative ^{99m}Tc-PSMA SPECT scan findings in one of the two cases, at a sensitivity of 50%. Figure 2 illustrates the difference in patient management between the two groups.

Discussion

An estimated 15% of men alive today will be diagnosed with prostate cancer.[14] Prostate cancer is responsible for 13% of all cancer deaths among men in South Africa and is the second leading cause of cancer deaths in males globally.[15] The disease can be risk-stratified according to its risk of progression and need for intervention, based on serum PSA level, clinical findings on a digital rectal exam, and a Gleason score from a prostate biopsy. Imaging plays an important role in the management and decision-making of patients diagnosed with intermediate- and high-risk diseases.

Table I: Baseline characteristics of patients

Characteristics		Value (*n*)
Number of patients		64
Age		63.6 (mean) (47–70)
PSA level (ng/mL)		40.2 (mean) (0.2–229)
	< 10	10
	10–20	18
	> 20	36
Gleason score	3 + 3	6
	3 + 4	8
	4 + 3	13
	> 4 + 4	37
Clinical stage	T1	15
	T2a	19
	T2b	13
	T2c	8
	> T3	9

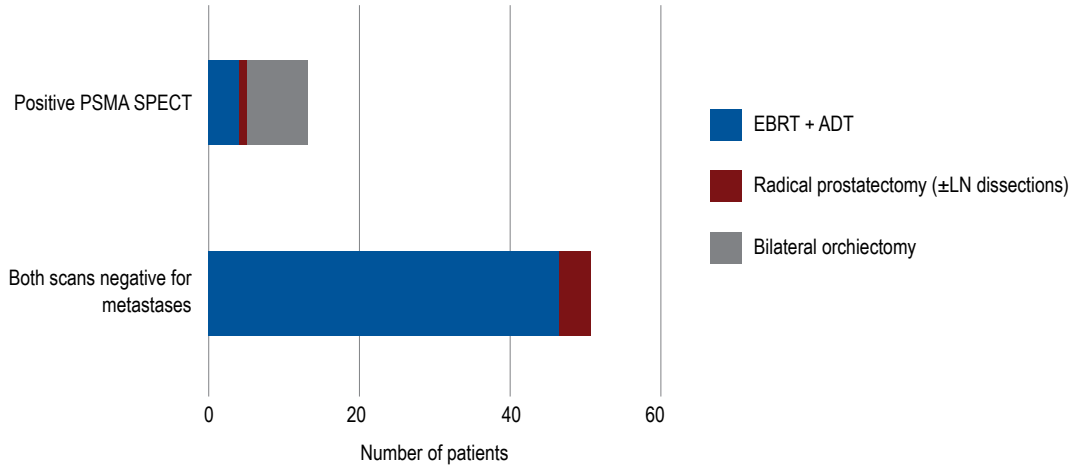

Figure 2: Bar graph illustrating the differences in patient management between the two groups

The 2022 NCCN guidelines indicate that for patients with high-risk prostate cancer, next-generation imaging (whole-body MRI, PSMA PET) should be performed if results from conventional imaging modalities (CT, multiparametric MRI, or bone scan) are negative or equivocal.[16]

In 80% of prostate cancer patients, metastases to the bone represent the initial and main metastatic site, making it one of the most important prognostic factors.[17] The clinical importance of early detection of bone metastases in patients with prostate cancer is to determine the overall survival of the patients and their quality of life. Patients who only have localised disease and no metastases may be offered radical treatment with curative intent. However, patients who have proven bone metastases should be offered less invasive treatment options to avoid unnecessary side effects.

^{99m}Tc-MDP is a nonspecific marker of osteoblastic activity that accumulates in response not only to tumours but also to degenerative joint disease, benign fractures, and inflammation.[18] Although bone metastases from prostate cancers are very heterogenic, the majority are described as “osteoblastic”, while pure “osteolytic” metastases are very rare. A bone scan only detects metastases at an advanced stage of tumour infiltration when an osteoblastic reaction to metastatic cell deposit has occurred. Studies have shown that a bone scan can be avoided with a serum PSA level less than or equal to 20 ng/ml.[19] The main problem with a bone scan has been its lack of sensitivity and specificity, leading to questions raised regarding its diagnostic effectiveness.[20,21]

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines on bone scan state that bone scintigraphy is usually appropriate for initial staging in patients for:

- determining intermediate-risk disease (stage T2, PSA level 10 ng/mL, or Gleason score ≥ 7);
- initial evaluation of patients with high-risk disease (stage T3, PSA level 20 ng/mL, or Gleason score 8);
- evaluation of patients with symptoms referable to the bones regardless of stage or risk;
- evaluation of patients in whom a change in treatment is anticipated;
- evaluation of patients presenting with a pathologic fracture; and
- evaluation of patients who are to undergo radium or other radionuclide bone therapy.

The guideline further states that bone scintigraphy is usually not appropriate for initial staging in patients with a low risk of metastatic disease (PSA level 10 ng/mL, Gleason score 6, and no other clinical signs or symptoms of disease).[20] In many cases, the region of interest cannot be definitively characterised as negative or positive for malignancy, and will routinely end up being characterised as equivocal, suspicious, or likely. Guidelines do not provide any technical recommendations for bone scans, and in many centres, a bone scan is limited to anterior and posterior planar images. A standard planar bone scan can be improved by single-photon emission computerised tomography (SPECT) on selected areas, enhancing both sensitivity and specificity for the detection of metastases.

PSMA has emerged as the pre-eminent prostate cancer target for diagnostic imaging, monitoring disease recurrence, and tracking disease progression. Nearly all adenocarcinomas of the prostate demonstrate PSMA expression in the majority of primary and metastatic lesions.[4,5] Studies have shown that PSMA expression is a significant prognosticator for disease outcomes.[6]^{68}Ga-PSMA PET/CT is superior to conventional imaging in the identification of nodal disease in patients with moderate- to high-risk prostate cancer.[7] ^{68}Ga-PSMA PET/CT has also been found to be superior to a bone scan in detecting bone metastases in prostate cancer.

However, ^{68}Ga-PSMA has significant shortcomings. Gallium-68 is obtained from a ^{68}Germinium/^{68}Gallium generator. As the generator reaches its end, it allows for a limited number of elutions per day, with each elution being sufficient for imaging up to two patients at a time. For institutions with limited access to gallium-68, this results in a barrier to patient workup. There are fewer PET cameras installed worldwide than most other imaging machines, which also limits the utility of this modality in daily clinical practice. This significantly limits the ability of ^{68}Ga-PSMA to meet the demand for imaging

in prostate cancer. Another issue is the high cost of ^{68}Ga-PSMA, readily impeding accessibility to the study.

These shortcomings have led to research into technetium-99m-labelled PSMA with HYNIC used as a chelator molecule. Technetium-99m is developed from a molybdenum-99 generator, which is capable of producing a large activity sufficient to prepare radiotracer for a large number of patients daily. The imaging is done with a gamma camera, which is also more readily available worldwide than PET cameras. The average cost per ^{99m}Tc-PSMA SPECT scan is R4 000.

Studies have shown that ^{99m}Tc-PSMA has a lower sensitivity for lesion detection compared to ^{68}Ga-PSMA PET/CT and recommend its use when ^{68}Ga-PSMA PET/CT is not available, or as part of monitoring the response to radioligand therapy in patients with lesions with known PSMA expression.[10] Furthermore, a comparison of these two types of imaging has shown that there is no significant difference between their detection of LN and bone metastases despite differences in spatial resolution.

There are studies that compare the ^{99m}Tc-PSMA scan with a bone scan. Rathke et al. found that PSMA scintigraphy demonstrated a reduced number of equivocal findings compared to a bone scan.[22] PSMA resulted more often in tumour-typical appearance, while MDP bone scan lesions were scored as equivocal or presumably benign. The sensitivity of PSMA in detecting bone lesions was 92%, compared to 76% for the MDP bone scan. Kabunda et al. concluded that the ^{99m}Tc-PSMA scan was comparable to a bone scan in the detection of bone metastases with the additional benefit of providing information on visceral disease.[23]

Available literature indicates that PSMA-targeted radiotracers are superior to conventional imaging, including a bone scan, in the workup of patients with prostate cancer. It has a higher pick-up rate for both skeletal and non-skeletal metastases. Given the limited diagnostic effectiveness of bone scans used in isolation, specifically their poor detection rate in the setting of men considered for radical treatment of organ-confined prostate cancer, and the aforementioned advantages of PSMA, this study sought to review the management of patients with high-risk and high-tier intermediate-risk prostate cancer, who have had a less well-studied form of the PSMA scan – the ^{99m}Tc-PSMA SPECT – following a negative ^{99m}Tc-MDP bone scan. We retrospectively reviewed whether or not these patients still underwent radical treatment after these findings or were offered alternate management modalities instead.

The discussion highlights that a bone scan is considered the gold standard imaging modality in the workup for metastases in this patient cohort, as per guideline recommendations, and is still being used worldwide. The problem with a bone scan is that it lacks sensitivity at lower PSA levels, and studies are often "indeterminate". PSMA has emerged as a far more sensitive and specific modality in the workup of metastases but is not yet standard practice. Furthermore, most studies supporting PSMA have looked at ^{68}Ga-PSMA PET/CT, whereas our study looked at the slightly less sensitive yet much more cost-effective and readily available alternative – the ^{99m}Tc-PSMA SPECT.

This study aimed to compare ^{99m}Tc-PSMA SPECT to bone scans, as there is a paucity of data comparing these two modalities head-to-head. Only one study made such a comparison, but in that setting, patients were already known to have bone metastases. This study involves patients who are workup naïve.

The results from this study confirm that ^{99m}Tc-PSMA SPECT is more sensitive and specific than a bone scan in detecting metastases. The major drawback of completely switching from bone scans to PSMA-based studies has been the cost and availability of ^{68}Ga-PSMA PET/CT, whereas ^{99m}Tc-PSMA SPECT is a less expensive and more readily available alternative that can overcome this issue. Consequently, it is recommended for clinical use for staging.

Conclusion

PSMA-targeted radiotracers are superior to conventional imaging, including a bone scan, in the workup of patients with prostate cancer. It has a higher pick-up rate for both skeletal and non-skeletal metastases. The major shortcomings are cost and availability. ^{99m}Tc-labelled PSMA is more cost-effective and readily available than ^{68}Ga-ligands targeting PSMA, at the expense of diagnostic sensitivity. There is only one published study comparing PSMA scintigraphy with an MDP bone scan, although this was in a setting of known prostate cancer metastases. There are no studies available that compare the diagnostic accuracy of these modalities in the staging of patients with high-risk diseases. This is an area that has not yet been sufficiently explored, and it could potentially open up the possibility of incorporating PSMA scintigraphy as a standard modality in prostate cancer workup, and not only in the setting where conventional imaging is equivocal.

This study confirms that a ^{99m}Tc-PSMA SPECT scan is a valuable diagnostic tool in the workup of patients with high-risk and unfavourable intermediate-risk prostate cancer. Amongst the group of patients reviewed, this scan was able to identify 20% who are understaged by bone scan. This enabled a tailored approach to their management plan, and unnecessary morbid intervention could be avoided.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

The University of Cape Town HREC REF Number 526/2020.

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